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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/580,660	03/08/2007	Robert Hofmeister	DEBE:066US/10605466	1727

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EXAMINER	
NATARAJAN, MEERA	
ART UNIT	PAPER NUMBER
1643	

NOTIFICATION DATE	DELIVERY MODE
08/12/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/580,660	HOFMEISTER ET AL.	
	Examiner	Art Unit	
	MEERA NATARAJAN	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 January 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26 and 30-50* is/are pending in the application.

4a) Of the above claim(s) *30-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114 was filed in this application after appeal to the Board of Patent Appeals and Interferences, but prior to a decision on the appeal. Since this application is eligible for continued examination under 37 CFR 1.114 and the fee set forth in 37 CFR 1.17(e) has been timely paid, the appeal has been withdrawn pursuant to 37 CFR 1.114 and prosecution in this application has been reopened pursuant to 37 CFR 1.114. Applicant's submission filed on 11/23/2009 and 01/04/2010 has been entered.

2. Claims 26, 30-50 are pending.

3. Claims 30-50 have been withdrawn as being drawn to non-elected inventions.

4. Claim 26 will be examined on the merits.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 26 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a composition comprising a polypeptide comprising at least two antigen binding sites wherein said at least two antigen binding sites are located on a single polypeptide chain and wherein one antigen binding site specifically binds the human CD3 antigen and the other binding site specifically binds to the human CD19, said polypeptide existing in both monomeric and multimeric form, said

multimeric form constitutes no more than **10-15%** of the total weight of the combined monomeric and multimeric forms of said polypeptide, and said polypeptide comprises SEQ ID NO:1., does not reasonably provide enablement for said polypeptide, wherein said multimeric form constitutes no more than **3%** of the total weight of the combined monomeric and multimeric forms. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

7. The instant claim is drawn to a composition comprising a bispecific polypeptide wherein the multimeric form constitutes no more than 3% of the total weight of the combined monomeric and multimeric forms. The instant specification does not enable a person of ordinary skill in the art to make the invention commensurate in scope with the claim. The instant specification, on page 26, illustrate a table which shows the relative proportions of bispecific single chain polypeptide present in multimeric (dimer) and monomeric form. Table 1 indicates the lowest amount of multimeric (dimer) form constitutes no more than 10-15% of the total weight of the combined monomeric and multimeric forms. The specification goes on to disclose, "each bispecific single chain antibody with anti-human CD3 antigen binding specificity spontaneously forms significant amounts of multimeric species when left uncontrolled. The propensity to spontaneously form homodimers therefore appears to be a generic characteristic of the class of which the bispecific single chain antibodies examined here belong" (see p. 26, last paragraph below table). Applicants own disclosure indicate that it would likely be impossible to isolate a composition comprising the bispecific polypeptide claimed

wherein the multimeric form is no more than 3%, because of the "generic characteristic" of spontaneously forming significant amounts of multimeric species when left uncontrolled. Applicant's own example illustrated in Table 1 indicates the lowest amount of multimeric form to be 10-15% (for which they are enabled for). The instant specification does NOT provide any working examples wherein a composition comprising the bispecific polypeptide claimed has no more than 3% of multimeric form. It is believed, based on applicant's own disclosure, that even after isolating (purifying) the separate, monomeric and multimeric forms, the monomeric forms would almost instantly form homodimers and therefore making it highly difficult to isolate a population of only monomers.

8. Therefore, applicants are only enabled for a composition comprising a polypeptide comprising at least two antigen binding sites wherein said at least two antigen binding sites are located on a single polypeptide chain and wherein one antigen binding site specifically binds the human CD3 antigen and the other binding site specifically binds to the human CD19, said polypeptide existing in both monomeric and multimeric form, said multimeric form constitutes no more than **10-15%** of the total weight of the combined monomeric and multimeric forms of said polypeptide, and said polypeptide comprises SEQ ID NO:1.

Claim Rejections - 35 USC § 103

9. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

11. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Dorken et al. (US Patent 7112324). *(It is noted the following rejection is directed towards the enabled scope of the claim as recited above.)*

12. The claims are drawn to a composition comprising a polypeptide comprising at least two antigen binding sites wherein said at least two antigen binding sites are located on a single polypeptide chain and wherein one antigen binding site specifically binds the human CD3 antigen and the other binding site specifically binds to the human CD19, said polypeptide existing in both monomeric and multimeric form, said multimeric form constitutes no more than **10-15%** of the total weight of the combined monomeric and multimeric forms of said polypeptide, and said polypeptide comprises SEQ ID NO:1.

13. Dorken et al. teach "single-chain multifunctional polypeptides comprising at least two binding sites specific for the CD19 and CD3 antigen" (see Abstract). Dorken et al. teach a polypeptide with binding sites specifically to human CD19 antigen and wherein

said polypeptide has a sequence that is 100% homologous to SEQ ID NO: 1 (see attached alignment). Dorken et al. is silent in regards to the percentage of multimeric form versus monomeric form.

14. It would have been *prima* facie obvious to one of ordinary skill in the art at the time the claimed invention was made to determine the percentage of multimeric versus monomeric form of a composition comprising the polypeptide taught by Dorken et al. to be no more than 10-15% multimeric. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success based on the teachings of Dorken et al., because the methods of purification taught by Dorken et al. are similar to those provided in the instant specification and therefore would result in isolating a composition comprising the same percentage of multimeric/monomeric form. Based on the teachings provided in the instant specification, and the generic characteristic of spontaneously forming homodimers, the methods of purification taught by Dorken et al. would result in a bispecific polypeptide composition comprising no more than 10-15% of the total weight of the combined monomeric and multimeric forms of said polypeptide.

Response to Arguments

15. In the appeal brief filed 11/23/2009, Applicants argue that a careful reading of the description of Example 6 of Dorken et al. provides that the "purity of the column fractions assessed by reducing sodium dodecyl sulfate, thus if one were to follow the specific teachings of Example 6 of Dorken et al., multimer and monomeric bispecific antibody constructs could not be distinguished for the simple reason that the multimeric proteins would have all been dissociated into monomeric proteins. Thus, the results of

this assay are meaningless when assessing what percentage of multimer exists." This argument has been carefully considered but not found persuasive.

16. Applicants continue to contradict themselves by first indicating that the claimed bispecific antibody spontaneously forms significant amounts of multimeric species, but then secondly claiming a composition containing no more than 3% multimeric form and arguing that Dorken et al. teach a composition comprising the bispecific antibody in only the monomeric form. Even if Dorken et al. isolated under reducing conditions the monomeric form of the bispecific antibody, it would spontaneously form dimers and would therefore result in a composition comprising no more than 10-15% multimeric form.

Conclusion

17. Claim 26 is rejected. No claim is allowed.

18. Any inquiry concerning this communication or earlier communications from the examiner should be directed to MEERA NATARAJAN whose telephone number is (571)270-3058. The examiner can normally be reached on Monday-Thursday, 9:30AM-7:00PM, ALT. Friday. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on 571-272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for

published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MN

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643